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Multicompartment Kinetic Models for Lead

I. Bone Diffusion Models for Long-Term Retention

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The long-term retention of lead in bone poses a number of difficulties for the usual multicompartment models. The use of diffusion models based on exchange of lead between blood in canaliculi and the crystalline bone of the osteon allows a linear compartmental approximation suitable for statistical estimation of kinetic parameters in peripheral compartments. The model is applied to lead retention by beagle dogs. © 1985 Academic Press, Inc.

1. INTRODUCTION

Lead is a pervasive environmental hazard in industrialized societies. It is usually encountered as airborne lead from additives to gasoline, in lead paint, in food contamination from soldered containers, and in contamination of drinking water from industrial discharges. A host of personal patterns of exposure are known, including occupational exposures, cigarettes, consumption of illicitly distilled spirits, and lead pica. The patterns of exposure have been detailed in many reports, including those of the National Academy of Science–National Research Council (NAS–NRC, 1972; 1980). A key issue in the regulation of environmental lead is the establishment of dose–response relationships between time-varying patterns of exposure to lead and biological precursors of adverse health effects. The purpose of this note is to extend some previous analyses to more complex models for the kinetics of lead.

Most of the adult body burden of lead is stored in the bone tissues. While the quantity of lead stored in the teeth is only a small fraction of the total lead burden, tooth lead constitutes a uniquely accessible indicator of cumulative lead exposure (Steenhout, 1982). Not all of the hard tissues of the body are permanent sinks for lead, however. While bones retain a large fraction of their lead burden for many years, another significant fraction of their temporary lead burden may be returned to the blood over an interval comparable to the residence time of lead in other tissues, up to 100 or 200 days. Linear compartmental models for lead retention and distribution in man have been developed by several authors (Rabinowitz *et al.*, 1976; Bernard, 1977; Batschelet, 1979). A compartment is assumed to be an homogeneous and well-mixed physiological pool that supports no concentration gradients internally so that ion transport appears to be nearly instaneous within the compartment. Blood and soft-tissue compartments appear "fluidlike" on time scales of a month or two. But lead retention in bone is another matter. Ions that have entered the bone matrix tend to travel through that matrix by a process of diffusion, and diffusion of ions through a crystalline matrix can

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be slow. In rather general terms this appears to explain the very long retention times for lead in the body, since lead has been observed to behave similarly to the alkaline earth metals such as calcium, strontium, barium, and radium that are known as "bone seekers." It would be more precise to say that these metals are *bone volume seekers*, in contrast to the bone surface seekers such as plutonium and other actinide elements.

There have been few efforts to incorporate bone volume seeking metals into compartmental models in which a number of peripheral soft-tissue compartments are also present. Marcus (1977, 1979) has presented a mathematical formalism using semi-Markov processes. This methodology may be useful for modelling and simulation, but poses formidable difficulties in statistical estimation of the unknown kinetic rate parameters. It is precisely these rate parameters which are needed in order to estimate the potential effects of various time-varying exposure patterns on critical peripheral target organs (e.g., brain, marrow) in which high concentrations of lead may accumulate and interfere with normal physiological processes of the central nervous system and hematopoeietic system. We have therefore developed a physiologically plausible model for bone diffusion that is more useful for estimation of kinetic parameters.

2. A MODEL FOR DIFFUSION IN BONE

Many of the basic ideas here have been described by Marshall and Onckelinx (1968). Bone surface includes the periosteum exposed to extracellular fluids, the endosteal surface at the bone marrow, the surfaces of the trabeculae, and (if present) the Haversian and Volkmann canals. The bone volume includes the osteocytes, their lacunae, canaliculi, bone crystal, and the organic matrix. From (Vaughan, 1970):

> The blood-vessels that nourish the bone run in the canals of the Haversian systems. . . . At a little distance from each canal is what is called a cement line across which the canaliculi do not communicate. The area of bone around each Haversian system bounded by a cement line is known as an osteon.

The radius of an osteon in cortical bone is on the order of 100 μm or less, but there is a great deal of variation in the size of the Haversian canals and osteons. In the diffusion model considered by Marshall and Onckelinx (1968), it is claimed that the ions must ultimately reach the bone volume by passing from the blood vessel in the Haversian canal through tiny canals (canaliculi), and that the passage from a canaliculus into the surrounding canalicular territory can be described by a cylindrical diffusion equation. A typical canaliculus in mouse bone has a radius about 0.075 μm, and the "limit of canalicular territory" has a radius of about 0.85 μm in their model.

Bone surface seekers are affected primarily by two processes: resorption (destruction or removal of bone to plasma) and apposition (bone surface formation due to deposition of new bone) which is very important for children. Deposition occurs relatively slowly in cortical bone in adults, but more rapidly in trabecular bone. The analogous processes in bone volume are diminution and augmentation

(both of which are modeled here by exchange with blood and extracellular fluid). (This description follows Marshall (1969).)

Compartmental models for alkaline earth metals, especially calcium, have been developed. Marshall (1969, p. 61) exhibits 10 such models; see Jung *et al.* (1978) and Heaney (1976) for critical reviews and references. None of these models directly incorporate bone volume diffusion. Groer and Marshall (1973) did consider diffusion as an alternative model for calcium exchange with serum at the bone surface, and found that the short-term kinetics of calcium exchange at resting bone surfaces could be far better described by a simple one-compartment model than by a model of calcium diffusion directly into the bone at the surface. However, in order to test this hypothesis they assumed the form of the serum concentration $X(l,t)$ was a power function

$$X(l,t) = 27.11\ (10)^{0.25}\,(t + 10)^{-0.25}\,(3000)^{1.3}\,(t + 3000)^{-1.3} \text{ (for dogs)}$$

$$X(l,t) = 20.83\ (100)^{1.2}\,(t + 100)^{-1.2} \text{ (for rabbits)}$$

where t is in minutes and X is surface activity of the tracer isotope. The duration of the experiments was about 400 hr (dogs) and 48 hr (rabbits). The use of power functions for $X(l,t)$ was not explained, and indeed cannot be explained on the basis of a linear compartment model. The diffusion model for bone volume seekers is a useful alternate explanation.

The numerical values of the physical constants strongly suggest that we consider the primary mechanism of transfer of metals to bone volume to be the exchange between blood in canaliculi and bone crystals in the canalicular territory (see Fig. 1). The radius of the canaliculi is taken as about $a = 0.075$ μm, which is the inner radius of the canalicular territory volume in an assumed cylindrical cross section, and the outer radius of the canalicular territory is about $b = 0.85$ μm. If ions were deposited only near $r = a$, most ions would return rapidly to the blood. But some ions would enter the interior of the canalicular territory and then exit only after an extended random walk through the crystalline matrix of the canalicular territory, either through some other canaliculus or through the Haversian canal. The other canaliculi are distributed more or less randomly in the matrix. In a dense network of canaliculi, the canalicular territory is in the shape of a polygonal prism surrounding each canaliculus. We believe that a useful first step can be made by approximating these polygonal prisms by circular cylinders of radius b, with the understanding that b is itself somewhat variable. The inaccuracy introduced by this approximation is not large compared to other uncertainties.

The diffusion constant D (area per unit time) provides crucial information on the time scale of the process. Groer and Marshal (1973) suggest that $D = 10^{-16}$ cm^2/sec (as order of magnitude approximation); thus the typical time constant for random walk must be on the order of $b^2/D = 7.225 \times 10^7$ sec = 2.29 years. The time scale for the canaliculus itself is only $a^2/D = 6.5$ days.

This is the heart of the difficulty in assuming that bone is a single homogeneous well-mixed compartment. The spatial location of the metal ion in bone is important, and an ion located inside the canalicular territory may take many years to

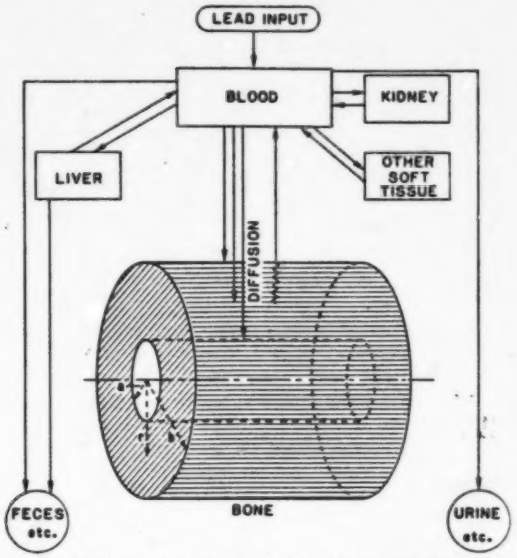

FIG. 1. Schematic model for lead kinetics in which bone is represented as an extended cylindrical "canalicular territory."

escape through some canaliculus or through the Haversian canal. Escape is possible, however, so that lead sequestered in bone at any age (especially in childhood) becomes a significant endogenous lead supply and contributor to blood lead later in life.

In order to develop a mathematical model for lead ions in the body, it is necessary to specify the ion transport processes involved in all compartments. These are assumed to be:

(a) cylindrical diffusion of ions in the bone volume;
(b) ion escape at the boundaries of canalicular territory,
(c) ion exchange with blood at the canaliculus, and
(d) transport between blood, soft tissues, and boundaries of the canalicular territory in bone.

Cylindrical diffusion processes are described in several books, but Carslaw and Jaeger (1959) is a comprehensive reference. Let t denote time and r the distance from the center of the canaliculus, as in Fig. 1.

Let $Q(r,t)$ be the concentration of metal ions at radius r at time t. The basic diffusion equation is

$$\partial Q(r,t)/\partial t = D\,\{\partial^2 Q(r,t)/\partial r^2 + (1/r)\,\partial Q(r,t)/\partial r\}. \quad (1)$$

We first specify the outer boundary conditions for loss of ions from the canalicular territory. The radius b serves only to scale the diffusion process, since a completely homogeneous diffusion into a completely homogeneous medium with regularly spaced canaliculi (e.g., on a square or triangular lattice) would have zero

concentration gradient along the surface of the polygonal prism marking the boundary between adjacent canaliculi. Because the loss of ions is not homogeneous, we will assume there is a first-order concentration gradient at radius b.

$$\partial Q/\partial r = -cQ/b \tag{2}$$

where c is a dimensionless gradient flow parameter that can be adjusted to fit the data.

For ion loss on time scales of a few weeks to many years, we may assume that most ions returning to the blood from the bone matrix do so through the same canaliculus by which they were initially deposited, but some ions may return to the blood by diffusion through the bone matrix to some other canaliculus or through the Haversian canal. The canaliculus is assumed to be a hollow cylinder of radius a. There is a little loss of accuracy in modeling the kinetics of long-term diffusion by assuming a relatively thin canaliculus with $a = 0$, since the diffusion transit time across the canaliculus is so short (about 1 week).

It is also convenient to assume simple first-order kinetics for the exchange of lead between blood (or the diffusible plasma component in blood) and the other soft tissues, as well as the blood–bone exchange at the canaliculus. Linear kinetic models are defined by the constant rate of fractional transfer of lead from compartment j to compartment i, here denoted $k(i,j)$. This assumption has been explored in detail in (Marcus, 1985a) using the data in (Rabinowitz *et al.*, 1976). We found that the first-order linear kinetic model with constant $k(i,j)$ cannot be rejected at blood lead concentrations less than 30 μg/dl. We also found (Marcus, 1985b) that lead in human blood appears to follow nonlinear kinetics at much higher blood lead levels, say in excess of 60–80 μg/dl; the analyses were based on data in DeSilva (1981). In this note we will assume linear blood and tissue kinetics, implicitly assuming lead exposure is not excessive.

An explicit mathematical development for bone diffusion is given in (Marcus, 1983). The basic ideas can be expressed by equations for the rate of change of bone lead concentration at the canaliculus, $Q(0,t)$, and among the soft tissue and blood compartments. Let $X(i,t)$ be the quantity of lead in some nonbone compartment i at time t, where $i = 1, \ldots, n$. Bone is $i = n$. Then

$$\begin{aligned} dQ(0,t)/dt = {} & (\text{rate of absorption of lead from blood at the canaliculus}) \\ & + (\text{rate of diffusion of lead into canaliculus from bone volume}) \\ & - (\text{rate of resorption of lead from bone to blood}) \\ & - (\text{rate of diffusion of lead into bone volume from canaliculus}) \end{aligned} \tag{3}$$

$$\begin{aligned} dX(i,t)/dt = {} & (\text{rate of lead absorption into compartment } i \text{ from other tissue}) \\ & + (\text{rate of absorption directly into } i \text{ from canaliculus}) \\ & - (\text{rate of flow from compartment } i \text{ to other soft tissues}) \\ & - (\text{rate of loss of lead to bone directly from compartment } i). \end{aligned} \tag{4}$$

The mathematical expressions for $Q(0,t)$ and $X(i,t)$ are complicated, using an infinite sum of exponential functions of time. In practice these equations can be well approximated by a compartmental model with a finite number of pools, i.e., a finite number of exponential compartments. The key to doing this involves

analytical approximation of the solutions $\theta(h)$ or eigenvalues of the diffusion equation (1) with boundary condition (2), and $a = 0$.

The assumed conditions for lead ion loss at the boundary of the canalicular territory determine the mathematical form of the eigenvalues $\theta(h)$. With the preceding assumptions, the eigenvalues $\theta(h)$ are the infinitely many solutions to the positive solutions to the equation.

$$\theta(h)\, J_1\,(\theta(h)) - c\, J_0\,(\theta(h)) = 0 \tag{5}$$

where c is the dimensionless parameter in (2), and $J_n\,(x)$ is a Bessel function of order n. Convenient approximations for $\theta(h)$ have been developed by Professor James A. Cochran of Washington State University and are described elsewhere (Marcus, 1983). The following even simpler approximations will be used here:

$$\theta(j) = \mathrm{D}\, a(j)^2/b^2 \tag{6}$$

where

$$a(1) = 2\,(2c)^{0.5}/(4 + c)^{0.5} \qquad a(j) = (j - {}^3/_4)\,\pi \text{ for } j = 2, 3, \ldots . \tag{7}$$

For $c < 1$, the approximation is accurate to with 2%. There are thus some regression coefficients $A(i,j)$ that depend on the linear kinetic model for soft tissue, on the component approximation, and on the initial conditions such that we can approximate the long-term retention by

$$X(i,t) = A(i,1)\exp(-\theta(1)t) + \mathrm{A}(i,2)\exp(-\theta(2)t) + \ldots \tag{8}$$

$$Q(0,t) = A(n,1)\exp(-\theta(1)t) + A(n,2)\exp(-\theta(2)t) + \ldots . \tag{9}$$

A technique for fitting the coefficients $A(i,j)$ and estimating the parameters $k(i,j)$, D/b^2, and c is described below.

3. FITTING THE DIFFUSION MODEL TO DATA

In order to use conventional computer programs such as SAAM 27 (Berman and Weiss, 1978) to fit a compartmental model to data, it is necessary to estimate the nonbone fractional transfer rates $k(i,j)$ for $i,j = 1, \ldots, n - 1$, the rate coefficient D/b^2 for bone diffusion, and the dimensionless coefficient c that measures the gradient for ion loss at the canalicular boundary. The following approximation allows these computer programs to estimate fractional transfer coefficients $k(n,i)$ from tissue into bone and $k(i,n)$ for loss from bone to tissue.

Assume that bone exchanges only with a blood or blood serum pool in which $i = 1$ denotes the blood compartment. If there were no diffusion, then $k(n,n) = -k(1,n)$. However, each value of h determines an eigensystem of size n with transfer coefficients $k(i,j)$ except for $k(n,n) = -k(1,n) - \mathrm{D}\,\theta^2(h)/b^2$. This suggests absorption be partitioned among the various components $h = 1, 2, 3, \ldots$ corresponding to the eigenvalues $\theta(h)$ of the diffusion equation, which can be done in three steps: (a) Omit compartment n and replace it by "bone components" $n + h$, $h = 1, 2, \ldots m$. (b) Replace the parameter $k(n,1)$ for bone absorption of tracer from blood. Let $k(n + h,1)$ be the absorption into bone component h, where the total rate $k(n,1) = k(n + 1,1) + k(n + 2,1) + \ldots$ is kept the same. (c) Replace the normal loss rate $k(1,n)$ by $k(1,n) + \mathrm{D}\,\theta(h)^2/b^2$ in bone component

$i = n + h$. This represents combined loss of tracer from bone due to normal processes such as bone resorption, as well as the return of tracer to blood by slow diffusion to the canalicular boundary at b. The number of components m can be increased until the model fits the data.

The approximation thus consists in replacing the bone diffusion model with n compartments by a conventional compartment model in which there are m peripheral mammillary pools, each representing an eigenvalue component h. This is shown symbolically in Fig. 2.

4. LEAD KINETICS IN BEAGLE DOGS

There is relatively little experimental data that can be used to simultaneously estimate all of the parameters in this model, since observations are required both for short-term kinetic parameters affecting blood and tissues, and for long-term retention. Short-term experiments usually involve serial sacrifice of the experimental animals and determination of tissue concentrations by autopsy. Long-term studies often involve radioisotope tracers with determination only of whole-body

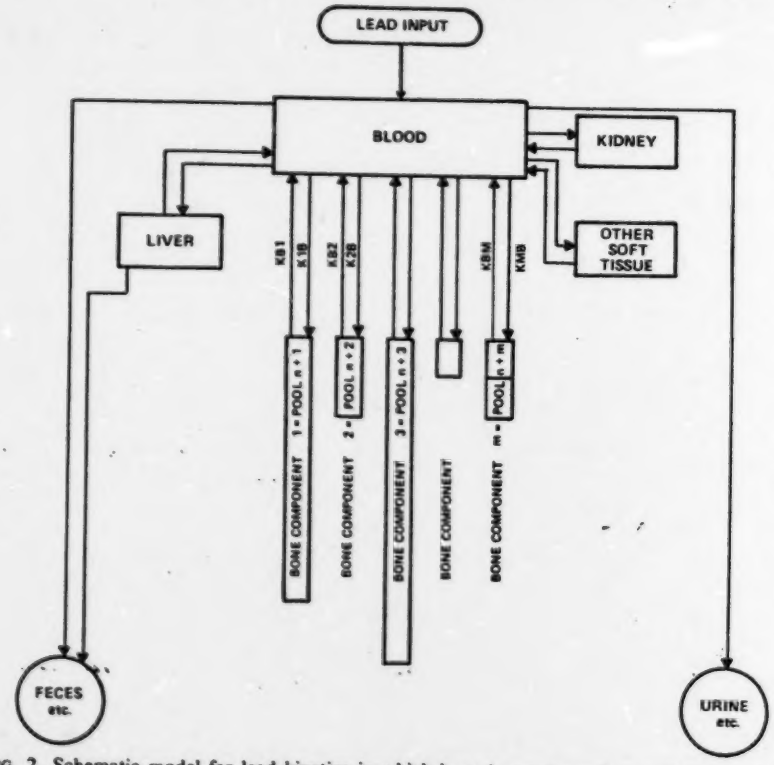

FIG. 2. Schematic model for lead kinetics in which bone is represented as a sequence of bone "components" based on eigenvalues of the diffusion model. KMB is the transfer rate from blood to bone component M to blood.

retention, blood concentration, and possibly excretion. One study which allows estimation of both short-term and long-term kinetics was developed at the University of Utah (Lloyd *et al.*, 1970; 1975; 1982). Beagle dogs were injected with ^{210}Pb and observed for several years. Three dogs in the study, all from the same litter, were injected intravenously with carrier-free ^{210}Pb. The dog labeled T2L5 was sacrificed at 28 days after injection, whereas T1L5 survived for 1497 days (4 years) and T3L5 for 1100 days (3 years). Whole-body and blood lead were reported separately for each, cumulative fecal and urinary excretion as an average for the three dogs, and liver, kidney, skeleton, and other tissue concentrations for T2L5 at 28 days. Because the dogs were littermates, it was assumed that the average fecal and urinary excretion data and the T2L5 tissue data were representative of the group. However, there were sufficient differences in blood lead and whole-body retention that the kinetic models were fitted to data on each individual dog in order to estimate between individual differences within a single litter.

We note that only direct measurement of skeletal lead was in dog T2L5 at 28 days. Since the skeleton already held 63% of the remaining burden at that time, it was reasonable to assume that most of the remaining burden was in bone thereafter.

Two models were fitted to data from dogs T1L5 and T3L5. The first was a conventional compartmental model that was also fitted to T2L5, as shown in Table 1. The second model was the bone diffusion approximation, as shown in Table 2. The parameters were estimated with the SAAM 27 program (Berman and Weiss, 1978). Several passes through the data were required to obtain a good fit, both in terms of model structure and estimation of parameters. It was possible to estimate parameters for compartments that could not be directly observed, including "other (soft) tissues," and two additional (presumably bone) compartments with long retention times of about 60 and 3000 days (see Fig. 3). The initial

TABLE 1
KINETIC PARAMETERS FOR COMPARTMENTAL MODEL IN BEAGLE DOGS

From/To	Dog T1L5		Dog T2L5		Dog T3L5	
Blood/liver	0.830	(0.184)	0.694	(0.107)	0.497	(0.129)
Blood/kidney	0.260	(0.183)	0.336	(0.171)	0.332	(0.183)
Blood/other tissues	0.161	(0.086)	0.031	(0.043)	0.098	(0.067)
Blood/feces	0.0638	(0.0085)	0.0609	(0.0062)	0.0596	(0.0063)
Blood/urine	0.0482	(0.0021)	0.0397	(0.0016)	0.0391	(0.0016)
Blood/bone ? (deep)	0.0372	(0.0021)	0.0339	(0.0203)	0.0337	(0.0026)
Blood/bone ? (shallow)	0.0644	(0.0057)	0.0636	(0.0249)	0.0586	(0.0046)
Liver/blood	0.341	(0.071)	0.354	(0.058)	0.252	(0.061)
Liver/feces	0.0473	(0.0050)	0.0379	(0.0061)	0.0418	(0.0050)
Kidney/blood	1.716	(1.090)	2.601	(1.292)	2.647	(1.465)
Other tissues/blood	0.237	(0.096)	0.077	(0.095)	0.188	(0.095)
Bone (deep)/blood	0.000302	(0.000039)	0.000301	(0.000329)	0.000476	(0.000080)
Bone? (shallow)/blood	0.0159	(0.0020)	0.0160	(0.0138)	0.0135	(0.0018)

Note. Values presented are estimated kinetic parameters in units of $days^{-1}$; values in parentheses are standard errors. Data are from Lloyd *et al.* (1970, 1975).

TABLE 2
KINETIC PARAMETERS FOR COMPARTMENTAL MODEL WITH BONE DIFFUSION IN BEAGLE DOGS

From/To	Dog T1L5		Dog T3L5	
Blood/liver	0.870	(0.077)	0.750	(0.075)
Blood/kidney	0.327	(0.050)	0.266	(0.042)
Blood/other tissues	0.171	(0.032)	0.145	(0.032)
Blood/feces	0.0647	(0.0076)	0.0635	(0.0070)
Blood/urine	0.0491	(0.0017)	0.0424	(0.0015)
Blood/bone (j = 1)	0.0377	(0.0057)	0.0350	(0.0052)
Blood/bone (j = 2)	0.		0.	
Blood/bone (j = 3)	0.0662	(0.0099)	0.0665	(0.0100)
Blood/bone (j = 4,5)	0.		0.	
Liver/blood	0.354	(0.036)	0.387	(0.042)
Liver/feces	0.0473	(0.0049)	0.0410	(0.0052)
Kidney/blood	2.025	(0.253)	1.980	(0.257)
Other tissues/blood	0.244	(0.039)	0.245	(0.045)
D/b^2 (diffusion scale)	0.000321	(0.000050)	0.000290	(0.000047)
c (gradient coefficient)	0.532	(0.083)	0.967	(0.151)

Note. Values presented are estimated kinetic parameters in units of days^{-1}; values in parentheses are standard errors. Data are from Lloyd *et al.* (1975).

estimated standard error of the initial parameter estimate was always set to 100% of the initial parameter value. The standard errors of the final estimates were almost always less than 50%, except for dog T2L5 for which there were only 28 days of data.

The bone diffusion model provided a good fit to the data as did the usual compartmental model (Figs. 4–7). For T1L5 the error sum of squares for the

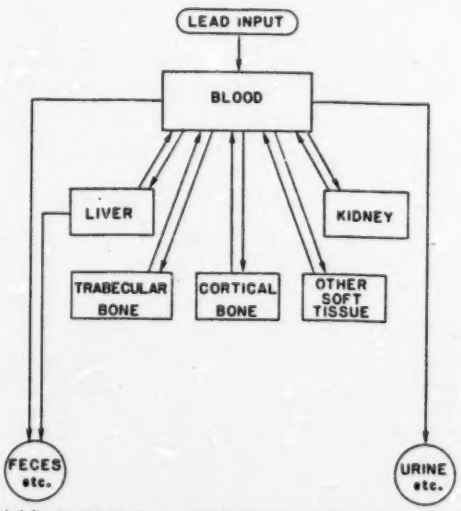

FIG. 3. Schematic model for lead kinetics in which bone is represented as a compartmental structure with two bone pools.

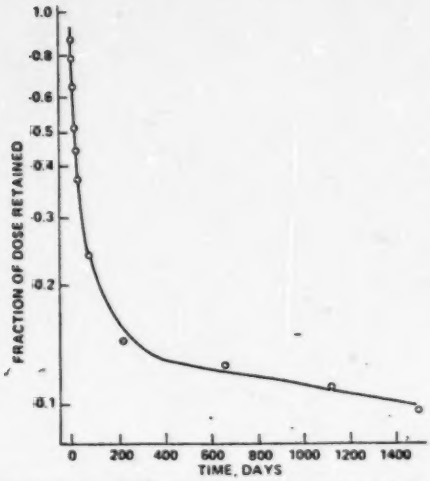

FIG. 4. Observed and predicted fraction of lead dose in blood for beagle dog T1L5.

diffusion model and the ordinary model (in $\%^2$) were 5.84 and 5.96, respectively, and for T3L5 were 3.69 and 3.93, respectively. While the bone diffusion model was not strikingly superior overall, it was certainly no worse than a good compartmental model—even with the constraints in time scales for diffusion imposed by the cylindrical diffusion model. The diffusion model did have more adjustable parameters, however.

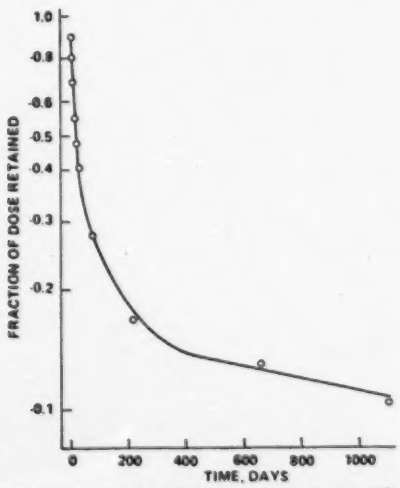

FIG. 5. Observed and predicted fraction of lead dose in blood for beagle dog T3L5.

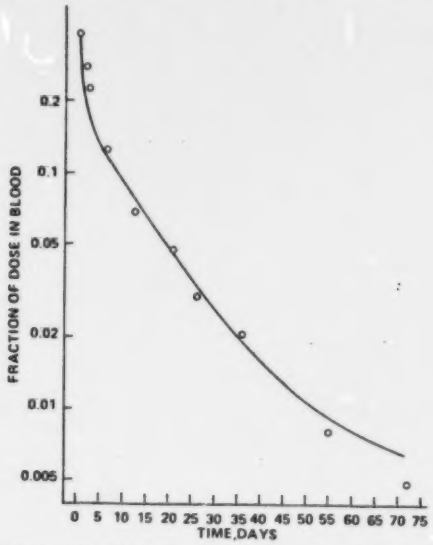

FIG. 6. Observed and predicted fraction of lead retention in body for beagle dog T1L5.

5. WHOLE-BODY LEAD RETENTION

There are substantial experimental difficulties in obtaining time series data on lead concentrations in peripheral tissues other than blood for a single subject or experimental animal. Tissue concentration data at time of autopsy may provide

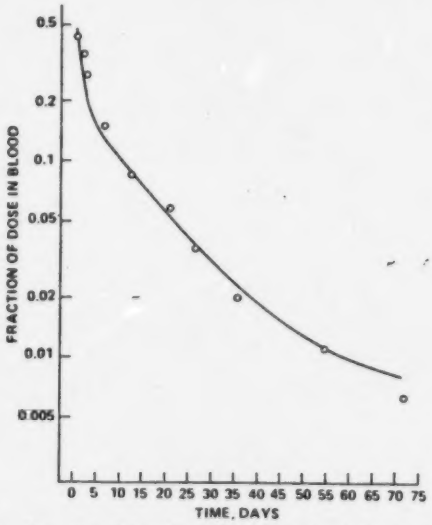

FIG. 7. Observed and predicted fraction of lead retention in body for beagle dog T3L5.

very complete information about organ burdens at some point in time, but very little information about kinetic parameters that are needed to model the changes in organ burden due to exposure to time-varying environments. The use of a sample of animals sacrificed at different times provides a cross-section of organ burdens across some population, but this may not tell us about any given individual since the variation in internal kinetic parameters may be very large even among animals of the same strain. In order to estimate the population variability in these kinetic parameters and thus to identify the fraction of the population that may be most highly at risk to a given lead exposure, it may be necessary to use only the most readily accessible kinds of measurements—blood measurements in humans, and blood and whole-body retention in laboratory animals, here denoted $R(t)$.

In choosing a method for fitting available whole-body retention data we must specify the purpose for which the retention function is needed. If the only purpose is to provide as concise a summary of the data as is possible, then one might consider a generalization of the model proposed in Marshall *et al.* (1972) which is a combination of exponential and power functions of time t,

$$R(t) = \{A_1 \exp(-v_1 t) + A_2 \exp(-v_2 t)\}/\{1 + t/a\}^b + A_3 \exp(-v_3 t) \qquad (10)$$

in our notation; we shall call this the ICRP model. There is little doubt that this is the most parsimonious of the models that can be fitted to long-term retention data for lead (Hursh, 1973) and many other metals (Wise, 1974; Matsubara *et al.*, 1981). By use of a formal statistical decision criterion, the Akaike Information Criterion, Matsubara *et al.* (1981) found most of the exponential terms unnecessary for curve-fitting purposes.

Unfortunately, curve fitting is not the primary goal of the toxicokinetic data analysis. The purpose is, rather, to see what bounds can be put on the internal kinetic parameters that determine the distribution of lead to blood and other organs. It is thus necessary to work with a family of curves that can be sensibly interpreted in terms of internal mechanisms. In this regard there are few practical alternatives to the use of the familiar linear compartmental model (Jacquez, 1972). In a compartmental model with n pools or compartments, each compartmental retention function (and thus the whole-body retention function $R(t)$) will be the sum of, at most, n exponential functions; i.e.,

$$R(t) = A_1 \exp(-v_1 t) + A_2 \exp(-v_2 t) - \ldots + A_n \exp(-v_n t) \qquad (11)$$

The longest timescales will differ only slightly from the residence times of lead ions in the most long-lived compartments (e.g., cortical bone) and so $R(t)$ will provide at least some tentative information on internal kinetic parameters. It is known that determination of the parameters of the plasma clearance curve provides useful limits or bounds on some combinations of the kinetic rate parameters (Chau, 1977). A similar analysis may be applied to $R(t)$, but in models with a large number n of compartments these bounds may not be useful. However, the combination of blood lead observations with $R(t)$ and with certain noninvasive measurements such as hair loss, and fecal and urinary elimination of lead, may allow valid inferences about internal kinetics. We thus adopt the usual compart-

mental model leading to $R(t)$ as a mixture of exponential functions in Eq. (11) because the results can, in principle, assist in estimating internal distribution of lead.

A second reason for assuming $R(t)$ is an exponential mixture is that the slow rate at which lead is lost from bone is probably due to diffusion of lead ions through the bone matrix (Marshall and Onckelinx, 1968; Marshall, 1969; Wise, 1974). A cylindrical diffusion process introduces an infinite spectrum of eigenvalues (time scales), but only a few of these have large coefficients A_i so that even the power function diffusion model can be well approximated by a mixture of exponential functions with a small number n of components. Thus, there are both practical and theoretical reasons for restricting consideration to compartmental models like Eq. (11).

In order to study the distribution of population parameters for lead retention over long periods of time, it is necessary to have data on individual animals. Much of the data reported in the literature are based on averages from several animals. The requirements of long series of individual data points and a large sample led us to use published data on beagle dogs for these analyses. In addition to the detailed analyses for beagle dogs T1L5 and T3L5 reported previously, retention data were given for seven other beagle dogs for 3 to 9 years (Lloyd *et al.*, 1970; 1975; 1982). These dogs were from only three litters, however. Hursh (1973 and 1978) has provided data on two more beagle dogs.

An exponential mixture (Eq. (11)) was fitted to each of these data sets for n of 3–5. Initial parameter estimates were obtained graphically by "peeling," then BMD PAR nonlinear regression program (Dixon, 1981) with $1/R$ weighting. In view of the small numbers of observations for the nine beagles reported by Lloyd *et al.* (1975), the standard error estimates for at least some of the components are quite large. Furthermore, each of the beagles T15Q4–T21Q1 had at least one observation sufficiently deviant to be given reduced or zero weight. However, we set aside only those observations whose removal did not much change the estimated parameters but greatly reduced the estimated standard errors of the parameter estimates. The two beagles S and U for whom Dr. Hursh provided data had substantial variability in estimated $R(t)$, but also had such a large number of data values for $t > 7$ days that no single observation had much influence.

The parameter estimates for the 11 beagle dogs are shown in Table 3. There is considerable consistency among beagle dogs in that $R(t)$ shows three regimes at the longest timescales: (a) 7 to 17% of the lead is retained in a term with time constant >2200 days; (b) 5 to 35% of the lead is retained in a term with time constant 55 to 500 days; (c) 20 to 67% of lead is retained in a term with time constant 10 to 55 days. All of the data sets could be well described by three or four exponential terms, even when the number of data points was very large (dogs S and U). When plotted on a log–log scale, the exponential mixtures gave a surprisingly good straight-line approximation over a large range of t values and demonstrate that while the ICRP model or some similar power-function model may be very convenient, it is not required in order to obtain a close fit to the data.

An exponential model with three or four terms provided an adequate or very

TABLE 3
ESTIMATED PARAMETERS FOR THREE LONGEST EXPONENTIAL COMPONENTS IN WHOLE-BODY RETENTION FUNCTION FOR LEAD[a]

Litter	Dog	N[b]	T[c]	A_1	ν_1	A_2	ν_2	A_3	ν_3
1	T1L5	11	1497	15.08	0.0002884	37.54	0.01912	36.69	0.11255
				(0.55)	(0.0000359)	(3.78)	(0.00216)	(3.55)	(0.01686)
1	T3L5	10	1100	17.67	0.0004687	31.88	0.01527	42.25	0.09044
				(1.29)	(0.0000878)	(5.98)	(0.00378)	(6.08)	(0.01807)
2	T15Q4	9[d]	1628	15.14	0.0001078[e]	11.82	0.003421	39.63	0.02333
				(3.00)	(0.0001224)	(4.15)	(0.002348)	(3.37)	(0.00712)
2	T16Q2	9[f]	3136	12.35	0.0001860	16.83	0.004458	70.82	0.06212
				(1.05)	(0.0000408)	(2.29)	(0.001208)	(2.78)	(0.02171)
2	T17Q2	9[f]	3136	15.35	0.0001849	16.97	0.004808	67.68	0.03970
				(0.90)	(0.0000285)	(3.03)	(0.001333)	(3.54)	(0.00579)
3	T18Q2	9[g]	3136	9.66	0.0	24.76	0.003000	65.59	0.05154
				(0.64)	0.0	(3.10)	(0.000532)	(3.26)	(0.02066)
2	T19Q1	9[d]	3144	10.32	0.0	16.09	0.001561	73.59	0.03530
				(0.20)	0.0	(0.65)	(0.000106)	(0.71)	(0.00144)
2	T20Q1	9[d]	3144	10.68	0.0	16.16	0.002776	73.16	0.03422
				(0.49)	0.0	(3.46)	(0.000593)	(3.56)	(0.00559)
3	T21Q1	9[d]	3147	9.34	0.0	21.97	0.001709	68.69	0.04644
				(1.08)	0.0	(4.00)	(0.00454)	(3.86)	(0.01886)
	S	83	842	6.69	0.000190[e]	15.65	0.005437	32.12	0.04755
				(2.54)	(0.000466)	(1.65)	(0.001477)	(1.50)	(0.00513)
	U	72	679	8.66	0.000192[e]	17.45	0.006993	50.09	0.06755
				(2.61)	(0.000466)	(1.71)	(0.001778)	(1.78)	(0.00495)

[a] Values in parentheses are standard errors. Data on dogs T1L5–T21Q1 are from Lloyd *et al.* (1970, 1975); data on dogs S and U are from Hursh (1973).
[b] N: Number of data points in fit.
[c] T: Largest time in data set.
[d] Without observation at t = 187 days.
[e] Standard error of estimate exceeds parameter.
[f] Without observation at t = 357 days.
[g] Without observation at t = 585 days.

good fit for the whole-body retention function of lead to sets of 9 to 83 observations on 11 beagle dogs, for observation times from 7 to 3147 days after injection of the initial lead dose. The computer-optimized parameter estimates showed a considerable range of variation across these 11 dogs, but also showed a considerable degree of consistency in the estimated time scales. Thus, whole-body retention functions can be compared on a component-by-component basis among various individuals in a population. However, the differences in timescale parameters ν_i and coefficients A_i suggest that fitting retention functions to aggregated or averaged retention data may be relatively meaningless since the average of the parameters measured for each individual will differ from the parameters estimated from the averaged data.

These statistics can be used to estimate the diffusion parameters from the fitted exponential time scales v_j, using the eigenvalue approximations in Eqs. (6) and (7). Let $v_1 < v_2 < v_3$ be the three smallest washout rates that can be fitted to the data (with $1/v_j > 60$ days). Since for small c

$$v_1 = (D/b^2)\, 8c/(4 + c)$$
$$v_2 = (D/b^2)\, 25\, \pi^2/16 \quad \text{approximately}$$
$$v_3 = (D/b^2)\, 81\, \pi^2/16$$

then c itself can be approximated from the ratios of smallest washout rates

$$v_2/v_1 = (25\, \pi^2/128)\, (4 + c)/c,$$
$$c = 4/\{(128\, v_2/25\, \pi^2 v_1) - 1\}$$

or

$$v_3/v_1 = (81\, \pi^2/128)\, (4 + c)/c,$$
$$c = 4/\{(128\, v_3/81\, \pi^2 v_1) - 1\}.$$

This estimated value of c can be used to solve for D/b^2 from v_1. The method is illustrated in Table 4 for all of the 11 beagle dogs. Note that $v_1 = 0$ implies $c = 0$. The estimates derived previously from the detailed compartmental models for dogs T1L5 and T3L5 are well approximated from the very crude method used here, but only by assuming that the term involving the true v_2 has "vanished," i.e., corresponds to $A_2 = 0$. Therefore the second term in the exponential regression model fitted to the data is actually $A_3 \exp(-v_3 t)$, so that the ratio v_2/v_1 from Table 3 is in reality v_3/v_1. With this modification, the estimated values of c are

TABLE 4
ESTIMATES OF DIFFUSION PARAMETERS FROM LONG-TERM WHOLE-BODY LEAD RETENTION

		Assuming 2nd component		Assuming no 2nd component	
Dog	v_2/v_1	c	b^2/D (years)	c	b^2/D (years)
T1L5	66.30	0.120	2.21	0.416	7.15
T3L5	32.58	0.252	2.77	0.949	8.96
T15Q4	31.73	0.259	12.34	0.980	39.99
T16Q2	24.62	0.340	9.47	1.359	30.69
T17Q2	26.00	0.320	8.94	1.264	28.45
T18Q2	+/0	(0.)	14.07	(0.)	45.60
T19Q1	+/0	(0.)	27.05	(0.)	87.63
T20Q1	+/0	(0.)	15.21	(0.)	49.28
T21Q1	+/0	(0.)	24.70	(0.)	80.04
S	28.62	0.289	7.76	1.117	25.16
U	36.42	0.224	6.04	0.828	19.56

Note. Data are from Lloyd *et al.* (1970, 1975), Table 3, and personal communications from R. D. Lloyd and J. Hursh.

rather similar (about 0 to 1.36), small enough to justify the approximations used above. The diffusion timescales b^2/D are long and differ substantially from one animal to another, 7 to 88 years; however, they are much closer among beagle dogs from the same litter.

6. RESULTS

As shown in Table 2, the kinetic parameters relating blood, liver, kidney, and other tissues, and bone can be estimated with reasonable precision with this model. In particular, the diffusion scale D/b^2 and outflow gradient parameter c can be reasonably estimated and appear to be rather different in value for the two dogs. Of course, such estimates are highly sensitive to the few data values at large times t. It is of considerable interest that the input parameters are positive only for the longest timescale corresponding to $\theta(1)$ (about 3000 days) and the third longest timescale $\theta(3)$ (about 60 days). The input coefficients for $\theta(2)$, $\theta(4)$, and $\theta(5)$ are best estimated as 0. This suggests that, to a crude first approximation, we may assume initial deposition of lead in the canalicular territory close to radius a so that it is either eliminated quickly by return to the canaliculus, or eliminated very slowly after diffusion through the canalicular territory to the initial canaliculus. The other parameters for soft tissue distribution of lead are much the same in this model as in the usual compartmental model.

There is also reason to believe that parameters for whole-body retention reasonably estimate those that would be derived from data on blood, fecal and urinary excretion, and peripheral tissue concentrations if such are available. As an example, the kinetic parameters from the compartmental model for beagle T1L5 in Table 1 may be used to derive the model $R(t) = 15.13 \exp(-0.0002567t) + 24.17 \exp(-0.01217t) + 54.98 \exp(-0.07465t) + 2.25 \exp(-0.2725t) + 2.05 \exp(-1.205t) + 1.46 \exp(-2.706t)$. Note that the first three terms differ substantially from those in Table 3, but that the timescales are at least comparable. The longest term is the one best estimated in this example. Thus the information lost in using only $R(t)$ rather than the whole compartmental model may be substantial, but substantial information remains. On the other hand, the estimates of the gradient parameter, c, in Table 4 are highly consistent.

7. DISCUSSION

Physiologically plausible models can be fitted to data on the long-term retention of lead in mammals by use of standard methods of compartmental analysis. Using more realistic models for bone kinetics, it may thus be possible to answer questions about the mobilization of lead stored in bone pools long after acute or chronic exposure to lead has ceased. Some of the possible events that could increase lead flow are an increase in the diffusion parameter D (e.g., by osteoporosis), and an increase in the bone surface gradient parameter c by nutritional changes. The presence of large bone pools of lead in adults may provide yet another unexpected hazard caused by undue exposure to the metal, even if the exposures are low-level chronic doses that do not cause excessive blood lead levels at the time.

Long-term experiments on humans are not feasible. However, Steenhout (1982)

has demonstrated an epidemiologic approach to lead kinetics using teeth and bones. Our calculations suggest that a single exponential term (single bone component corresponding to the smallest eigenvalue) may indeed be an adequate description for bone kinetics in man on a lifetime scale, but additional components may be necessary on a 1-year scale.

Single exponentials for long-term retention in humans have also been proposed by O'Flaherty *et al.* (1982) and by Kang *et al.* (1983), using blood lead data on workers removed from occupational lead exposures by strikes or by medical removal protection programs. O'Flaherty *et al.* find a slight increase in the apparent residence time of lead in blood with increasing duration of exposure, a finding not replicated by Kang *et al.* Our analysis suggests that such an increase in residence time is possible because larger quantities of lead eventually diffuse to interior parts of the osteon. However, the time-scales described by O'Flaherty *et al.* are rather short (ca. 80 to 90 days) compared to those found by Kang *et al.* (ca. 160 to 250 days). By analogy with the beagle dog data, these time-scales probably do not correspond to the longest retention terms (i.e., $j = 1, 2$) but to the faster components ($j = 3, 4, 5$, etc.). Longer durations of exposure may thus increase the coefficients of the components, $j = 1, 2$, increasing the apparent half-life of the exponential mixture.

The approach outlined in this paper allows practical fitting of retention functions to models in which diffusion mechanisms play an important role. A class of problems in which this may be of use involves clearance of flow-limited substances by diffusion through an assumed spherical liver acinus (Norwich, 1982); Norwich and Siu, 1982). Our method allows the inclusion of other compartments as well, and does not require the prohibitively costly numerical solution of a diffusion equation at each iteration of the least-squares program that is used to estimate the unknown kinetic parameters. Our method may thus be useful for fitting other toxicokinetic models.

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